

Jonker, Leon, Todhunter, Jane, Robinson, Lesley and Fisher, Stacey (2020) Open-label, randomised, multicentre crossover trial assessing two-layer compression bandaging for chronic venous insufficiency: results of the APRICOT trial. *British Journal of Community Nursing*, 25 (Sup6). S6-S13.

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Title: An open-label, randomised, crossover trial assessing two-layer compression therapy bandaging (Andoflex TLC Calamine versus Coban2) in chronic venous insufficiency patients; results of the APRICOT trial.

Running title: Compression bandage-related patient feedback

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Acknowledgements:

We would like to express our thanks to Emma Mark, Laura Singleton, Zoe Saunders and Katherine Davidson from North Cumbria Integrated Care NHS Foundation Trust for their valuable contribution to delivery of the study. The authors would like to acknowledge the National Institute for Health Research for supporting the study.

Conflicts of interest: None of the authors have any conflict of interest to declare. None of the employees at Andover Healthcare contributed to or supervised any element of the study or its resulting manuscript.

Sources of funding: A non-restricted research grant, through provision of Andoflex TLC Calamine compression bandaging and a non-restricted grant was received from Andover Healthcare, now part of Milliken & Company.

Title: An open-label, randomised, multicentre crossover trial assessing two-layer compression therapy bandaging (AndoFlex® TLC Calamine versus Coban2®) in chronic venous insufficiency patients; results of the APRICOT trial.

Abstract

Background Compression bandaging is the mainstay therapy for chronic venous insufficiency and venous leg ulcers, but patient compliance can be challenging due to associated discomfort.

Aims Comparison of AndoFlex® TLC Calamine versus Coban2® compression bandaging in relation to patient comfort and related pruritus symptomology, with severity of pruritus scale as primary outcome.

Methods Multi-centre, prospective, non-blinded, randomised controlled crossover trial involving 39 randomised participants. Two periods for chronic venous insufficiency patients, to wear either AndoFlex® TLC Calamine or Coban2® for three weeks each.

Findings No significant differences in validated pruritus outcome measures were observed, including a non-significant treatment effect for the severity of pruritus scale (n = 35 trial completers, p-value 0.24, Wilcoxon test). However, after trying both bandages, 21 out of 35 patients (60%) definitely preferred AndoFlex® TLC Calamine whereas 4 patients (11%) definitely preferred Coban2®.

Conclusion AndoFlex® TLC Calamine compression bandage therapy is preferred by the majority of patients, although this observation could not be confirmed using validated patient-reported outcome measures for pruritus. Further research is indicated to establish if patient preference translates into favourable clinical outcomes.

Background

Chronic venous insufficiency (CVI) is associated with a host of different conditions, ranging from varicose veins to venous leg ulcers (VLU). It is well-established that a 'Western' lifestyle of obesity and lack of exercise increases the risk of CVI; in the USA, for example, it is the seventh leading cause of disability (Danielsson et al, 2002; White, 1993). Similar high incidences are found in Europe, with a prevalence of varicose veins occurring in more than 10% of adults in Scotland (Bergan et al, 2006). VLUs are the most common type of leg ulcers, affecting 1-3% of the population over 60 years and this incidence is expected to increase with an ageing population (SIGN, 2010; Graham et al, 2003). Each year, the NHS spends approximately £2.3bn – £3.1bn (at 2005-2006 cost) on dressings and associated products, equating to 3% of the total estimated health expenditure (Posnett and Franks, 2008). Furthermore, patients with wounds cost the NHS up to £5 billion more per annum than matched control patients (Guest et al, 2015).

The mainstay of treatment of VLUs is the reversal of venous hypertension through compression bandaging, to be followed by intervention to treat the venous reflux (O'Brien et al, 2012). However up to 15-30% do not respond to this current gold standard treatment and remain unhealed even after 6 months of treatment (O'Meara et al, 2009; Moffatt et al, 2006). Treatment success in CVI is highly dependent on achieving high levels of patient compliance. Unfortunately, compliance rates are often poor in this population (Heinen et al, 2007). Minimising the frequency of undesirable effects related to compression bandaging

may make the therapy more comfortable. Apart from bandage slippage, the most common undesirable effects of wearing compression bandaging are skin-related; pruritus develops in as many as 1 in 3 patients and can be a reason for non-compliance in 1 in 5 patients (Ayala et al, 2019; Stansal et al, 2013; Reich-Schupke et al, 2009). Some decades ago, Unna's boot was developed; this concerned a gauze dressing impregnated with calamine, a compound substance of primarily zinc oxide and less than one percent ferric oxide (Rubin et al, 1990). Technology has advanced and current compression bandaging products tend to be two-layer short stretch compression bandaging systems (Hanna et al, 2008). Unna's boot has been shown in the past to be effective at controlling pruritis in different conditions, including burns-related long-term itch (Shohrati et al, 2007). Recently, Andover Healthcare (part of Milliken & Company) has introduced a two-layer short stretch compression bandage that contains Calamine, though its performance in relation to other existing compression bandage products has not been appraised (Todd, 2019). The aim of this randomised, controlled, crossover trial was to determine patient experience and preference concerning two types of two-layer compression bandaging, namely Andover Healthcare's AndoFlex® TLC Calamine and 3M's Coban2® system in a population of patients who require compression bandaging due to CVI, with severity of pruritus as the primary outcome.

Methods

Study design and patients

The APRICOT pilot study (A Patient and clinician Reported Impression of COmpression Therapy study) is a multi-centre, prospective, controlled crossover trial of two types of compression bandaging therapy, involving patients deemed to benefit from this

intervention. Patients enrolled were from four NHS organisations in England; one vascular department in a hospital Trust and three GP practices. Full research governance clearance was obtained from the National Research Ethics Service (reference 18/WA/0383), Health Research Authority (reference 252438) and the NHS Trusts; the study was also registered on the International Standardised Clinical Trial Number registry under reference ISRCTN95282887. The crossover study design was opted for to measure the degree of itchiness caused by either of the compression bandage brands in the same patient, and to be able to measure patient preference. The premise of the study was not for each patient to commence with no pruritus present at all or to reduce a degree of pruritus to zero. A washout or non-compression period was not feasible for this patient population, but the risk of carry-over effect was minimised by having a 3-week trial period per compression bandage brand and then applying questionnaires that cover a shorter period.

Eligibility criteria were patients with mental capacity and command of English who were aged 18 years or older, with a clinical diagnosis of chronic venous insufficiency and CEAP clinical score of C2 or higher (Eklof et al, 2004). Additional exclusion criteria were limited life expectancy such as palliative care, history of not being able to tolerate compression, calamine or zinc oxide, and an ankle brachial pressure index (ABPI) of < 0.5. Written informed consent was obtained, and thereafter participants were allocated 1:1 at random to commence either Coban2® or AndoFlex® TLC Calamine first, using a non-restricted randomised sequence generated for the whole sample using a freeware randomisation programme called Randomizer.org. Sequential envelopes with each next randomisation allocation were used to achieve concealment – there was no block randomisation by recruiting centre. A member of the study team who did not see patients generated the

randomisation sequence, and clinical staff enrolled patients and assigned the participants to the interventions. Since the primary focus was symptomology and not wound healing, there was no prerequisite for patients to have an ulcer, and no stratification for ulcer size or chronicity took place. As the study involved compression bandages that looked different, it was not possible to achieve blinding for the participants, clinical, or research staff.

Intervention and outcomes

At baseline (week 0), patients - who either newly required or were already prescribed leg compression bandaging - were allocated to wear one brand of compression bandage for 3 weeks first (pre-crossover, i.e. up to week 3), followed by subsequently wearing the other second brand for 3 weeks (post-crossover, i.e. week 6). The standard choice of compression bandage outside the trial was Coban2®. Both 'Lite' (25-30 mmHg) and normal (35-40 mmHg) compression patients were invited to participate since they were administered the corresponding equivalent before and after crossover. Furthermore, Coban2® Lite and AndoFlex® TLC Calamine Lite, plus Coban2® and AndoFlex® TLC Calamine respectively, offer comparable compression. For all patients, current standard practice of applying emollient (Epaderm or Dermol in this study) before applying compression bandaging continued for all study participants and both pre- and post-crossover (Brown and Butcher, 2005).

At weeks 0, 3, and 6, clinical and patient related outcome measures were recorded. Pruritus was measured through patient feedback using the Severity of Pruritus Scale (SPS) score (Yosipovitch et al, 2017), visual pruritus score (Reich et al, 2012), and the 5-D itch score (Elman et al, 2010). Wound size was determined with the Pressure Ulcer Scale for Healing (PUSH) score tool, which is also validated for use on venous leg ulcers (Ratliff and Rodeheaver, 2005). Patient-reported quality of life in relation to their vascular disease was

measured using the Chronic Venous disease quality of life Questionnaire (CIVIQ-20) (Launois et al, 2010). The Venous Clinical Severity Score (VCSS) was used by the clinical staff to report on status of the venous insufficiency and related symptomology (Vasquez et al, 2010). Further patient feedback recorded included patient feedback on bandage comfort over the 3 weeks that it had been worn (including a survey list of symptoms, and severity if any of the symptoms experienced), plus patient preference concerning the two bandage brands at the end of the crossover trial when both brands had been worn. Any adverse events, withdrawal, lost to follow-up and VLU infection rates were also recorded. Serious adverse events were pre-defined in the protocol and the study was managed in accordance with good clinical practice.

Statistical analysis

Since pruritus has been reported as an undesirable effect by patients (Reich-Schupke et al, 2009), and one of the compression bandages in the trial contains Calamine with the aim to control this feature, this was used for a priori sample size calculations. With no pilot data available, an hypothetical distribution of responses on the SPS was used for sample size calculation purposes. The estimated clinically important difference for SPS is 20% (Yosipovitch et al, 2017). A minimum of 25 patients needed to be enrolled to achieve 80% power, 5% significance, at 20% attrition rate and a slightly more pronounced 30% difference between mild and moderate symptoms between the two different bandages (at each respective time point), whilst applying the Chi-squared test. To allow comparative analysis of before and after crossover periods, a per protocol approach was applied. The Mann-Whitney U-test was applied for the outcomes measures for individual time points, whereas

the Wilcoxon signed-rank test was used for paired analysis of combined week 3 and week 6 outcome data. Carryover effect was calculated by performing Wilcoxon test on the sum average for the Andoflex® TLC Calamine first group versus the Coban2® first group. Treatment effect was assessed by performing Wilcoxon test on the difference between week 3 and week 6 outcomes for the Andoflex® TLC Calamine group, and the difference between week 6 and week 3 for the Coban2® first group (Koch, 1972). Analysis for period effect was not performed due to relatively short intervention periods. Data was collated using Excel software and analysed with SPSS v20.

Results

From February 2019 to and including November 2019, 61 patients were considered of which 39 were randomised; data is presented in Figure 1. The vascular department enrolled 36 patients, and each of the three GP practices recruited one patient; recruitment was ended since the planned target had been reached (it was exceeded due to presentation of more suitable patients than anticipated in planned enrolment period). A total of 35 out of 39 (90%) patients completed the 6-week two-phase trial period. A single adverse event occurred, where a patient had to be taken off AndoFlex® TLC Calamine due to a mild skin reaction which could probably be attributed to the bandage. In Table 1, an overview is given of baseline patient characteristics for each respective 'first treatment' randomisation arm and for the study cohort as a whole. Patients who first commenced on AndoFlex® TLC Calamine were on average younger, but otherwise the treatment arms were similar. All participants, bar one, were instructed to wear the compression bandaging continuously in line with clinical needs. Table 2 shows how the performance of AndoFlex® TLC Calamine

compared to Coban2® as measured using validated questionnaires. These include measurement of pruritus (SPS tool, visual pruritus score and 5D itch score), patient-reported quality of life in relation to their chronic venous insufficiency (CIVIQ20), clinician score of severity of the patient's vascular disease (VCSS) and a semi-quantitative PUSH score on venous ulcer size. No significant carryover effect was observed for any of the outcome measures. The treatment effect observed for SPS was also non-significant at 0.24, and therefore no significant difference in pruritus levels was observed between the two compression bandage therapies. Similarly, no significant difference was observed for the other two validated pruritus measurement tools. In the case of the non-itchiness measures - ulcer size, venous disease symptoms and quality of life - a smaller score indicates a more favourable outcome. . Table 2 shows that a significant treatment effect was observed for Andoflex® TLC Calamine versus Coban2® in relation to PUSH score and VCSS. This suggests that Andoflex® TLC Calamine may be associated with accelerated improvement in clinical features of VLU.

Non-validated surveys were administered to participants when compression bandage was applied for the first time and at the end of each three week period. The instant reaction surveys were non-informative since all patients reported positively about the comfort and fit of the bandaging, regardless of the applied brand. At the end of the trial period for each bandage, the participants were asked to report whether they experienced symptoms that may be associated with wearing compression bandaging, and what the frequency and severity of said symptom was whilst wearing each brand of compression bandaging (responses for each brand of compression bandaging from the pre- and post-crossover trial phases were merged). Of the 11 symptoms assessed, 'pins and needles' were almost never

experienced by any participant, sweating was a rare occurrence and there were no patient-reported difficulties getting dressed with either bandage. Hardly any patients felt a degree of heaviness or burning sensation whilst wearing either compression bandage. Figures 2 and 3 summarise the data for the remaining six symptoms that were investigated. The occurrence of symptoms is shown in Figure 2, whilst Figure 3 depicts the severity of these symptoms. Itchiness was confirmed as the most common symptom experienced by patients, followed by three other symptoms: a sensation of constriction; pain; and movement restriction. Patients experienced pruritus more often when wearing Coban2® and the symptoms were more troublesome. Coldness was a symptom experienced when wearing AndoFlex® TLC Calamine in particular, though the symptoms were deemed mild.

To explore if there are any signs of impact on wound healing by either of the compression bandage brands, for all participants the PUSH score was recorded (score of nil for patients without an ulcer) at baseline, week 3 and week 6. Although the leg ulcers in the cohort that used AndoFlex® TLC Calamine first were on average significantly larger, this difference had reduced to a non-significant difference versus the Coban2® cohort by the end of week 3. However, when AndoFlex® TLC Calamine was used post-crossover, a no significant improvement versus Coban2® was observed both versus the other cohort within that timeframe and versus the pre-crossover period involving the same cohort of patients.

Figure 4 summarises the responses by patients concerning their preference for any of the two compression bandage brands that they wore in the preceding six weeks. Q1-Q9 corresponds to the nine questions in Table 3. Overall, more patients preferred AndoFlex® TLC Calamine; from a patient point-of-view it appears that the degree of comfort offered by AndoFlex® TLC Calamine was the main reason to prefer it over Coban2® (Q3, Q5, and Q9),

with pruritus control being a secondary reason (Q5). Patients were also offered the chance to write additional comments about their experience with wearing the two compression bandages. The most common free-text patient comments associated with wearing AndoFlex® TLC Calamine were that it felt 'cooling' (mentioned six times) and 'soothing' (noted five times). These observations were not made by patients when they wore Coban2®. A total of five nurses applied both compression bandage brands to the trial participants' legs. At the end of the trial they were asked whether they had a preference regarding the bandages. On a 5-point Likert scale, three nurses 'probably' preferred and two nurses 'definitely' preferred to use AndoFlex® TLC Calamine over Coban2®.

Discussion

Significant advances have been made in compression bandage technology, particularly with the progression from four-layer to two-layer designs. Unna's boot is a four-layer compression bandage treatment option which has since been surpassed in popularity by two-layer short stretch designs due to the improved application, although their respective wound healing efficacy is similar (De Carvahlo et al, 2018; Ashby et al, 2014). AndoFlex® TLC Calamine revisits the use of calamine in Unna's boot in the modern two-layer compression bandage design, and this study assessed patient feedback of said product versus the established Coban2® brand through a randomised crossover trial. This study shows that a) pruritus is the most common and most bothersome symptom associated with wearing compression bandaging and b) AndoFlex® TLC Calamine is preferred by patients for the degree of comfort provided, but no significant difference was observed in this study versus Coban2® when validated outcome measures for pruritus were applied.

AndoFlex® TLC Calamine was preferred over Coban2® by the majority of participants in this study, possibly due to the reduced itchiness and cooling/soothing effect reported by participants. A degree of carry-over effect, a known risk in crossover studies where there is no washout period possible (Mills et al, 2009), may have occurred since the carry-over p-values for pruritus surveys were close to the significance level of 0.05. Although the difference in pruritus levels between the two bandage brands was less obvious according to the outcomes measured with validated scales for itchiness, the anti-pruritic effect of Unna's boot has been demonstrated before in patients with sulphur mustard exposure.¹⁶ Zinc oxide, the main ingredient of calamine, is a recognised antipruritic agent and like calamine itself is applied for a multitude of disorders (Gupta et al, 2014; Mak et al, 2013).

Impregnation of textiles with zinc oxide, akin to the AndoFlex® TLC Calamine approach, is an emerging therapy modality for e.g. atopic dermatitis (Wiegand et al, 2013). In a previous study, two-layer Coban2® was preferred to the four-layer Profore system (Moffat et al, 2008), although pruritus was not assessed; bandage slippage was the key outcome measure in that study. In the present investigation the degree of bandage slippage was comparable between AndoFlex® TLC Calamine and Coban2® and less of an issue than itchiness, leg constriction and pain.

The outcomes for wound size (PUSH), clinical severity of venous disease (VCSS), and vascular-related patient quality of life (CIVIQ20) were favourable for AndoFlex® TLC Calamine in this study, with significant differences found for the former two. However, this has to be placed in context of the study design and applicable inclusion and exclusion criteria. The crossover design means that both 'Lite' and full compression patients could be enrolled in the trial, since they were allocated the same compression strength for each of

the two bandage brands. Since the primary objective was to assess pruritus and other patient-reported symptoms associated with compression therapy, some non-ulcer patients were included in the trial too. An efficacy trial for wound healing and venous insufficiency symptomology is indicated to determine if improved patient-reported comfort levels and indications of favourable healing associated with AndoFlex® TLC Calamine truly translate into a positive clinical response. Quantification of the wound size through wound tracing or digital measurement was not conducted for pragmatic reasons in this present study, but would have to be applied in a formal wound healing trial. Another limitation of the study includes a lack of blinding of participants and/or use of a blinded metrologist. Furthermore, although patients were recruited from different sites, the majority of patients (92%) were recruited from a single site.

This study has identified key patient-reported issues that may arise from wearing two-layer compression bandaging and this may aid clinical staff in clinics. Itchiness of the legs appears to be the biggest issue. The feeling of constriction, pain and movement restriction may occur in either AndoFlex® TLC Calamine or Coban2®, and one bandage may give better results than the other in those situations. Previous publications have previously reported that pain associated with having a leg ulcer is an issue, and that the degree of mobility whilst wearing compression bandaging is an important aspect considered by patients (Morgan et al, 2011; Walshe, 1995). Since in all patients but one, the compression bandaging was to be worn continuously, the impact of each bandage brand on therapy compliance rates was not assessed. However, compliance is a recognised issue.¹¹ Since a possible reaction to AndoFlex® TLC Calamine was seen with one patient, a patch test with the base layer could be performed if there are any concerns regarding adverse reactions.

However, published cases of reactions to calamine are rare, and usually involve the presence or application of another substance (Gupta et al, 2007; Praditsuwan et al 1995). In the present study, related to tolerability, one patient who could only tolerate Coban2® for two days before having it changed could manage to wear an AndoFlex® TLC Calamine bandage for a consecutive four days.

In conclusion, from a comfort perspective AndoFlex® TLC Calamine is preferred to Coban2® compression bandaging by patients. Pruritus levels appear low with AndoFlex® TLC Calamine, which supports the rationale of introducing Calamine to two-layer short stretch compression bandaging technology; however, the difference in pruritus levels as measured with validated outcome measures were non-significant compared to Coban2®. Further research is indicated to further explore the potential of AndoFlex® TLC Calamine to aid leg ulcer healing and wider clinical outcomes, through a non-crossover randomised controlled trial design, stratification by degree of compression ('Lite' and full compression), exclusion of non-ulcer patients, and a longer trial phase of – for example – 12 weeks. The putative contributory role of patient compliance with compression therapy should be explored too.

Keywords: chronic venous insufficiency; compression bandaging; pruritus; venous leg ulcer; wound care

Key points:

- Compression bandaging of the lower legs, using a two-layer short stretch system like Coban2®, is a core treatment modality for patients with leg ulcers due to chronic venous insufficiency

- Minimising patient discomfort related to compression bandaging is important to reduce the risk of non-compliance with compression therapy
- AndoFlex® TLC Calamine is a compression bandage system akin to Coban2® in terms of the degree of compression achieved; it does however, contain calamine in the skin-touching base layer.
- In this cross-over trial, patients found AndoFlex® TLC Calamine more comfortable than Coban2® ; however, not to a significant degree when measured with validated pruritus scales.
- Further research is indicated to investigate whether AndoFlex® TLC Calamine therapy can contribute to enhanced venous leg ulcer healing rates.

Reflective questions:

- Of the symptoms associated with two-layer compression therapy, evaluated through patient feedback in this study, which are the most common and most severe?
- What aspects of compression therapy are important to patients and may contribute to improved compliance?
- How may calamine impregnated bandage contribute to controlling undesirable symptoms associated with compression therapy?

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Figure 1, CONSORT flowchart for APRICOT trial

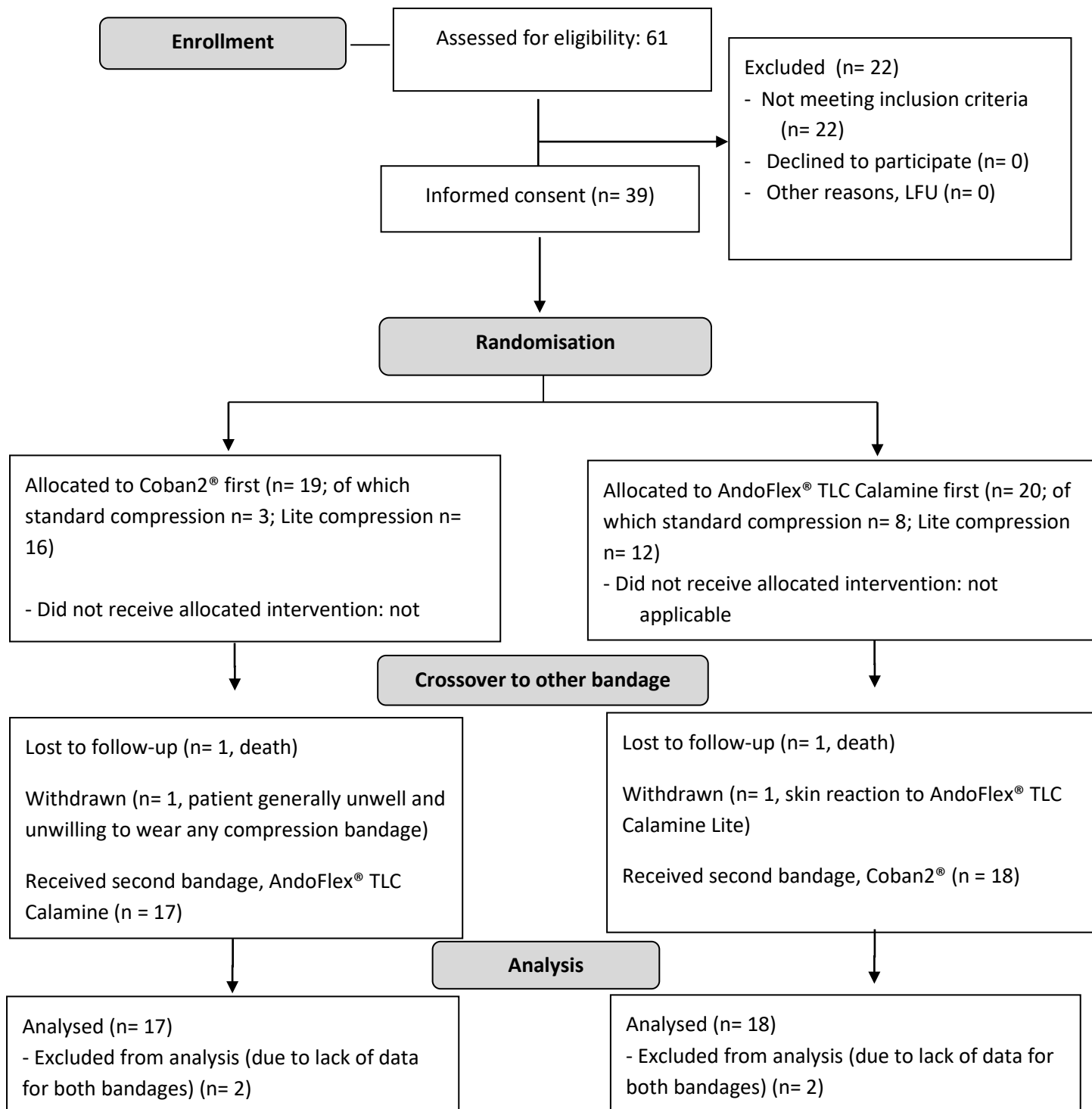


Figure 2, Patient-reported occurrence frequency of symptoms associated with compression bandage therapy

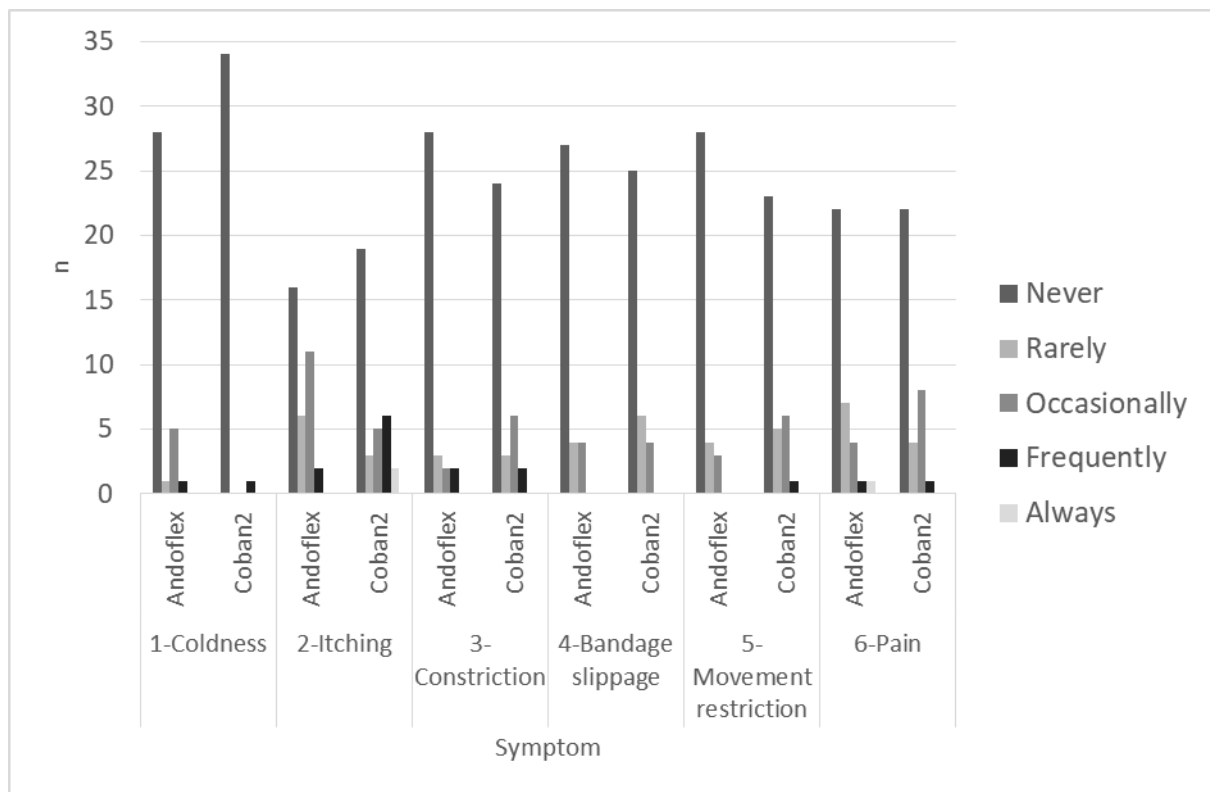


Figure 3, Patient-reported severity of occurring symptoms (see Figure 2) associated with compression bandage therapy

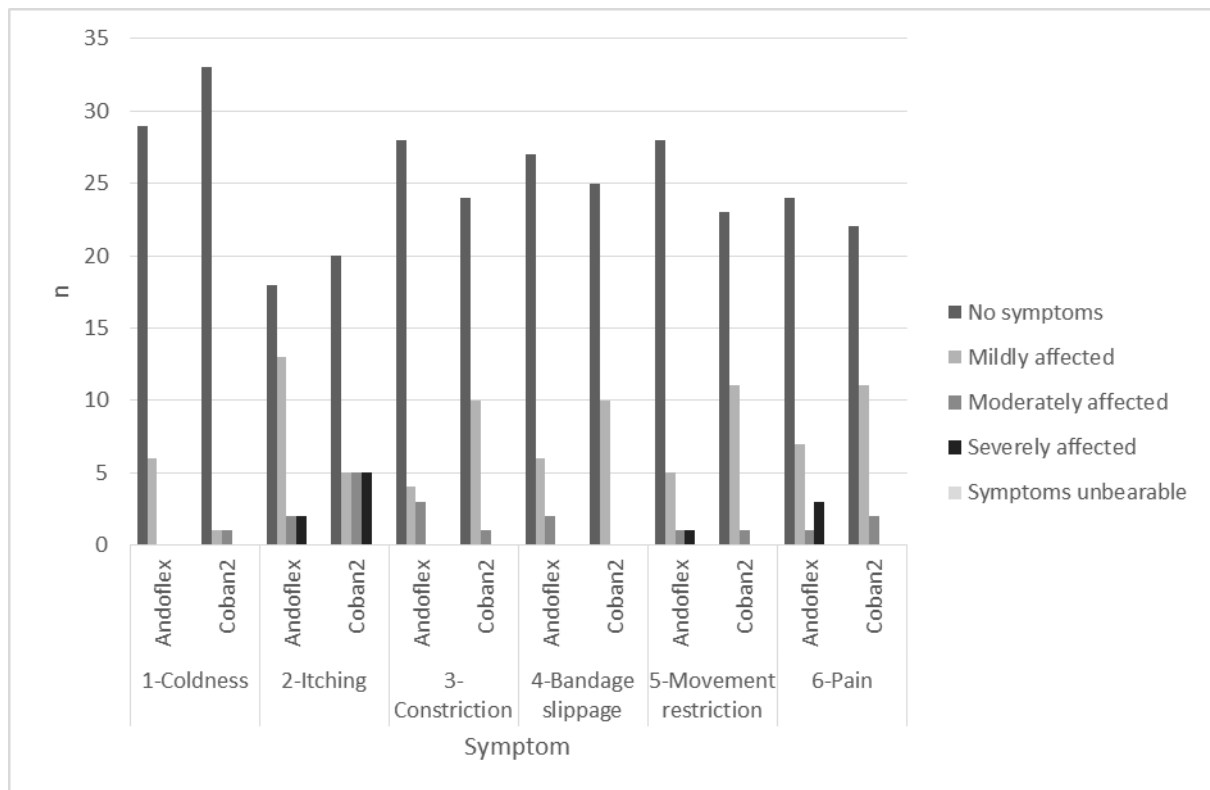


Figure 4, Patient preference questionnaire at end of trial of both bandages (see Table 4 for description of questions Q1-Q9)

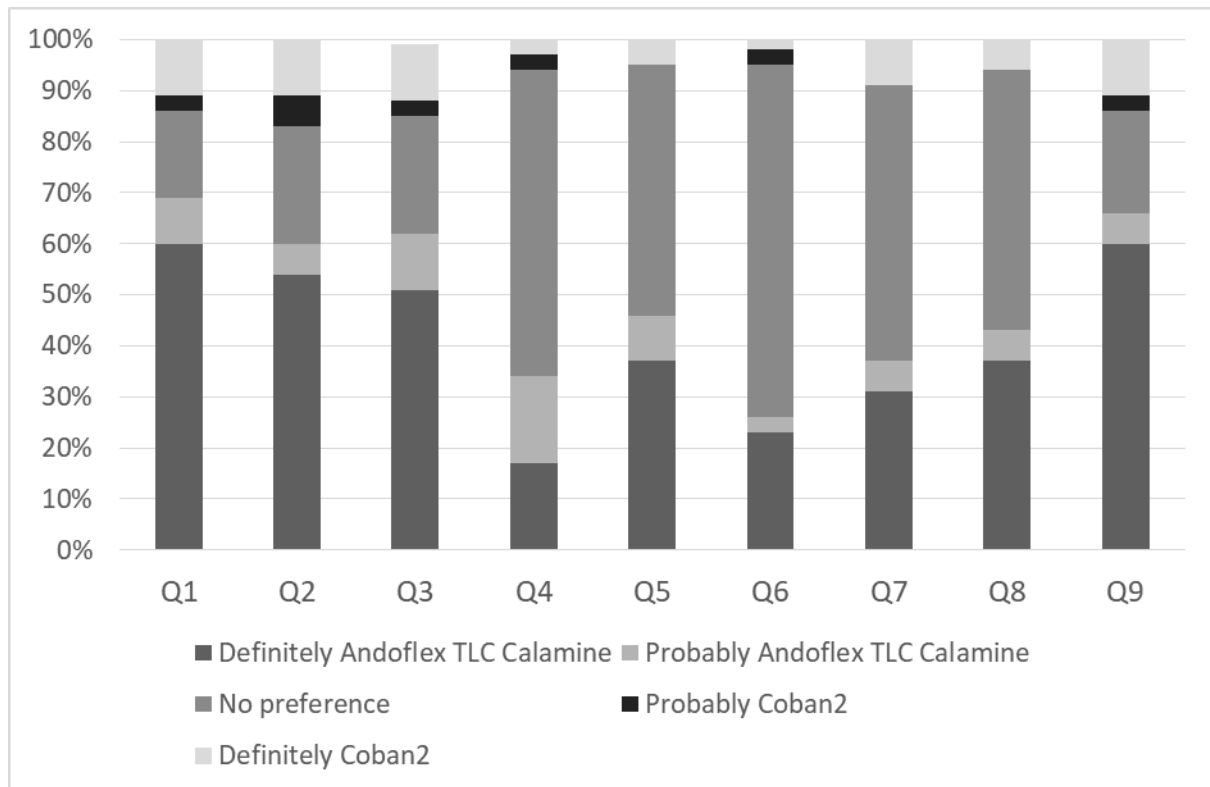


Table 1, Demographics and clinical parameters at baseline (trial completers only; normal and Lite compression patients combined)

Variable	Cohort		
	Coban2® first [n=17]	AndoFlex® TLC Calamine first [n=18]	Complete study population [n=35]
Age in yrs, mean (95% CI)	78 (74 to 82)	70 (63 to 77)	74 (69 to 78)
Sex, male (%) / female (%), n	8 (47%) / 9 (53%)	9 (50%) / 9 (50%)	17 (49%) / 18 (51%)
BMI in kg/m ² , mean (95% CI)	31 (27 to 35) [n= 16]	32 (29 to 36) [n= 14]	32 (29 to 34) [n=30]
Smoking status, never / ex / current, n	9 / 4 / 1 [n= 14]	10 / 2 / 2 [n= 14]	19 / 6 / 3 [n= 28]
Reason for compression bandaging, ulcer / post-surgery / conservative, n	13 / 2 / 2	16 / 1 / 1	19 / 3 / 3
Mobility status, w/o assist / w assist / unable to walk	8 / 4 / 3 [n=15]	9 / 6 / 0 [n=15]	17 / 10 / 3 [n =30]

Table 2, Measurement and comparison of outcome measures between Coban2® and AndoFlex® TLC Calamine

Outcome measure	Baseline, week 0			Week 3 (pre-crossover)			Week 6 (post-crossover)			Crossover analyses	
	AndoFlex® first (n = 18)	Coban2® first (n=17)	p-value*	AndoFlex® (n = 18)	Coban2® (n = 17)	p-value*	Coban2® (n = 18)	AndoFlex® (n = 17)	p-value*	Carryover effect, p-value**	Treatment effect, p-value**
Severity of Pruritus Score, median (IQR)	0.5 (0 to 1.3)	1 (0 to 2.5)	0.30	0 (0 to 1)	1 (0 to 2.5)	0.10	0 (0 to 1.3)	1 (0 to 1)	0.26	0.10	0.24
Visual pruritus scale, median (IQR)	2 (0 to 5)	5 (0 to 6)	0.35	0 (0 to 3)	4 (0 to 6)	0.28	0 (0 to 4)	1 (0 to 4)	0.26	0.17	0.23
5D itch score, median (IQR)	8.5 (5 to 12)	10 (5 to 14)	0.38	5 (5 to 9)	7 (5 to 12)	0.18	5 (5 to 9)	7 (5 to 10)	0.20	0.12	0.36

PUSH, median (IQR)~	10 (8 to 12.5)	8 (2.5 to 9)	0.010	10 (1 to 12.5)	7.5 (0 to 11)	0.54	7 (0 to 10)	0 (0 to 9)	0.15	0.49	0.002
VCSS, median (IQR)+	13 (10 to 17)	12 (11 to 17)	0.61	11 (7 to 16)	11 (8 to 13)	0.97	11 (5 to 14)	8 (5 to 12)	0.39	0.64	<0.001
CIVIQ20, median (IQR)	54 (31 to 74)	61 (46 to 67)	0.61	44 (25 to 61)	49 (29 to 54)	0.59	43 (23 to 54)	38 (29 to 54)	0.90	0.88	0.055

~ AndoFlex® n=17, Coban2® n=16; + AndoFlex® n=17, Coban2® n=17; *Mann-Whitney U-test; ** Wilcoxon signed-rank test; IQR, Interquartile

range

Table 3, Patient preference survey questions asked at end of trial (results summarised in Figure 4).

Question
1. Overall, the bandage of my preferred choice is:
2. I would recommend the following bandage to other patients:
3. The bandage that was most comfortable to wear was:
4. The bandage easiest to apply to my leg(s) - or applied by someone else - was:
5. The bandage that was easiest to move about in was:
6. The bandage that allowed me to use normal footwear/shoes the best was:
7. I had the <u>least</u> itchiness problems with:
8. I had the best night rest when I was using the following bandage:
9. The bandage that was the most comfortable for my skin was: